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Research Biopsies in Phase I Studies:

Views and Perspectives of Participants and Investigators

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The ethics of incorporating research biopsies into early-phase clinical trials is a pressing concern, particularly if the biopsy is mandatory. Molecular analyses for established driver mutations and putative but unvalidated biomarkers are often crucial to the understanding and development of novel therapeutic agents, making tumor biopsies an unavoidable requirement for achieving key scientific aims. Yet some commentators view mandatory research biopsies as coercive and suggest that they should be optional,[1] or at least optional until further data are obtained regarding their scientific usefulness.[2] Others argue that mandatory research biopsies can be ethical if specific conditions are followed.[3]

In addition to concerns about the scientific value of research biopsies are concerns about whether they offer benefits to individual research participants. Although the medical benefit of a research biopsy cannot be assured (since the benefit of the clinical trial is not assured), the potential for benefit exists.[4] Some research biopsies may be used to determine whether an individual meets the eligibility requirements of a clinical trial, to direct a trial's treatment, and/or to identify the toxicity profile of a trial intervention. Furthermore, standard-of-care clinical biopsies may also be performed in the midst of a research trial. This is a complicated situation to communicate to prospective research participants.

The suggestion that research biopsies may be medically beneficial to research participants is a relatively new contribution to the medical literature. This view is based on the assumption that entering a phase I trial can be beneficial[5] and, therefore, procedures that determine treatment on the trial may also be beneficial to research trial participants.[6] Of note, the consent template for phase I trials developed by the National Cancer Institute (NCI) does not clearly differentiate research biopsies that lack the potential for medical benefit for trial participants from those with that potential. The template contrasts “regular cancer care” procedures with “tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.”[7] The second description is silent about whether the research tests and procedures could benefit the trial participant.

Several guidelines and policies have enumerated requirements for ethically including a research biopsy in a clinical trial:[8] it must be necessary, with no good alternative, to provide data for an important scientific question;[9] risks must be minimized and reasonable in relationship to the scientific knowledge to be obtained;[10] and participants must understand if research biopsies are nonbeneficial[11] and what risks are associated with them.

To date, little is known about the views of research participants and members of the research team regarding the use of research biopsies in clinical trials. In one study, Agulnik and colleagues surveyed 10 trial participants who had undergone research procedures and 265 clinic patients who had not.[12] Nearly half of each group did not understand that no direct medical benefit to them would result from a research biopsy and assumed the information derived from the procedure would be used to guide their clinical care. Thirty-six percent of the clinic patients reported that a mandatory research biopsy in a clinical trial would discourage them from participating in the trial. Participants in the study by Agulnik and colleagues also had a tolerance for assuming high risk, with a quarter willing to accept a 5–10% chance of a major complication from a research biopsy. Perceptions of the riskiness of research biopsies were not studied.

The goal of this study was to test Agulnik's findings with a larger sample of trial participants, a key target population that needs to understand whether research biopsies have the potential to confer clinical benefit. Our primary aim was to describe phase I participants' understanding of whether a research biopsy offered them the prospect of medical benefit. We also endeavored to describe participants' views about biopsies—specifically, the benefits of biopsies, if any, and whether biopsies were acceptable, risky, or discouraged trial participation. Finally, we collected demographics and attitudes to see if any strong correlations with misunderstanding, acceptability, or riskiness existed. These data were supplemented with a review of the way investigators and consent documents present the risks and benefits of research biopsies.

Study Methods

Clinical Trial Participants

We interviewed and surveyed a convenience sample of participants in phase I clinical trials at a single institution with an active early drug development program. The interviews obtained qualitative data regarding 1) their understanding of the lack of direct medical benefit from research biopsies, 2) their understanding of the risk associated with biopsies, and 3) their views on the acceptability of undergoing a biopsy in the context of a clinical trial. These individuals (hereinafter respondents) were also asked one factual question: whether their trial had a mandatory or optional research biopsy. In addition, we collected extensive demographic and attitudes information, asking respondents about the strength of their religious or spiritual beliefs and the comfort they derived from them, their level of trust in medical research generally and in the physician who explained the phase I trial specifically, their perceived number of treatment options left, and their previous experience in research.

Since some of the respondents were enrolled in clinical trials that did not include research biopsies, we first read the following explanation to all of them in an attempt to get a standard response on the question of benefit:

> Some research includes biopsies so that scientists can study the tumor or bone marrow. Some of these biopsies help research on cancer but are not done to take care of patients. Those kinds of biopsies are research biopsies. In Phase I research, research biopsies are important so that scientists can learn about how new drugs act

> on cancer. But, on the other hand, patients have already gone through a lot. Please think about research biopsies as you answer the questions below.

After reading this statement, the interviewer described two kinds of biopsies, tumor and bone marrow. The interviewer asked respondents to identify the type of biopsy they had undergone in the clinical setting and prompted them, when answering the questions about their views of biopsies, to think about hypothetical bone marrow or tumor biopsies just for research, depending on the type of biopsy they had undergone for their cancer care. Since when estimating benefit, respondents may not intend to state population-level estimates, but rather express a belief such as "I am 95% confident that I will benefit," we asked respondents to estimate both their own personal benefit and the general, overall benefit, hoping to elicit a statement of belief with the first question and a statement of fact with the second.[13] We then asked respondents to describe the benefit from a research biopsy, if any was claimed. The first 33 of the 95 interviews did not include this last question, and therefore, the sample size was 62 for this particular analysis.

We counted a respondent as an "understander"—i.e., understanding the lack of benefit from research biopsies—if 1) the respondent estimated benefit to all patients as being zero, or 2) the respondent included altruistic benefits in his or her estimation of benefit. Our inclusion of altruistic benefit was based on the argument by Agrawal and colleagues that phase I trial participants' estimates of benefits may include nonmedical benefits.[14] To examine whether misunderstanding—that is, estimating benefit as being greater than zero and not listing an altruistic benefit—was associated with a particular subset of our respondents, we looked for associations between understanding and respondent demographics and attitudes.

Finally, since the type of biopsy in the respondents' trials might confound their answers to whether the biopsies offered benefit, and if so, what kind—even though the interviewer instructed respondents to consider only hypothetical research biopsies done to "help research on cancer but not done to take care of patients"—we examined whether the respondents' understanding or lack thereof was associated with the type of biopsy done in their trials.

We used the psychometric model[15] developed to characterize risks of technologies such as nuclear power and x-rays and behaviors such as smoking and skiing to gauge respondents' perceptions of the riskiness of biopsies. Following this model, as used by Benthin,[16] we identified risk factors pertinent to research biopsies and eliminated nonapplicable factors such as risk to peers, admiration, newness, and catastrophic impact. The Benthin factors relevant to research biopsies—knowledge, fear, personal risk, benefits versus risk, seriousness of effects, information value, and personal control—were supplemented by an additional factor that is not found in the risk literature but that arguably is a risk factor for research biopsies: pain. On a 10-point Likert scale, some questions indicated low risk by a high number response (10 = knowledge important) and some by a low number response (0 = no pain). For the analysis, numbers were transposed so that low numbers consistently represented low risk. As is standard, the mean for each question was determined to characterize the perception of risk. The total risk appraisal was calculated as the mean of each respondent's mean for the eight factors.[17]

Acceptability was gauged by willingness to enroll in a clinical trial with a mandatory biopsy and to undergo an optional biopsy, and whether the reasons given to explain these responses expressed positive or negative views of research biopsies.

Research Team

We also surveyed the physicians, research nurses, pharmacists, and research coordinators who had open phase I studies. The survey asked for estimates of the frequency of participant

misunderstanding regarding benefits from research biopsies and about strategies for conveying information about their potential risks. We obtained permission from the investigators (physicians and the phase I research nurse) and several of their patients to audiotape phase I informed consent conversations. Only discussions about trials with research biopsies were analyzed for this report. We assessed whether 1) the discussion was an early introduction to the trial with no discussion of specific procedures, or 2) the procedures were discussed and the discussion was a) clear, b) fairly clear, or c) unclear regarding the distinction between a research procedure and clinical care.

Trial respondents tended to view research biopsies as acceptable, though they did not succeed in identifying the lack of benefit of these biopsies.

Consent Document Review

The consent documents for the respondents' trials were reviewed for 1) use of the NCI template, and 2) clarity of the biopsy description.

Statistical Analysis

For all phases, all qualitative data were analyzed using standard qualitative methodology. For the trial participant component of the study, the phase I nurse-practitioner, an ethics fellow, and the principal investigator separately coded the first five interviews and surveys and then met to create a standard code book. The three then used the codebook to code the three open-ended questions analyzed in this report: concerns about and perception of the benefits of biopsies and views about voluntary biopsies. Agreement was reached on all but eight of the codes. The three coders discussed and reached consensus on two of these eight. The remaining six were resolved by the director of the phase I unit, a doctor of pharmacy. For the research team component of the study, two ethics fellows independently categorized each conversation using categories agreed upon before analysis: clear, fairly clear, or unclear in the explanation of the biopsy, focusing specifically on whether the conversation was clear about the type of biopsy (research or clinical care) and whether the biopsy had the potential for benefit. The two ethics fellows agreed on the categorizations of all investigator conversations, so the principal investigator only spot-checked three. For the review of the consent documents, two ethics fellows independently categorized them using categories agreed upon before analysis: 1) follows the NCI template, or 2) does not follow the NCI template and is either clear or unclear about the type of biopsy (research or clinical care) and whether the biopsy had the potential for benefit. There was substantial disagreement about whether the NCI template was used (7/37 consent documents), which we resolved by restricting the NCI template category to consent documents that used the NCI language verbatim. There was one disagreement on the clarity of the discussion, which was resolved by the principal investigator.

The continuous variables, such as age, were presented with mean and standard deviation; t-tests compared two different groups, and F-tests compared multiple groups. The categorical variables were presented with frequency and compared with chi-square tests. The Fisher exact test was used instead when the numbers in some cells of contingency tables were less than five. The significance levels were set at 0.05 for all tests. The SAS statistical package V9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all data management and analyses.

Study Results

Clinical Trial Participants

A convenience sample of 95/114 (83%) phase I participants agreed to and completed an interview and survey. The 19 who declined were more frequently female than were

respondents (p = 0.029). The median age of respondents was 57 (range 28–85). About half were men (56%), college graduates (50%), and had household incomes of $60,000 or more (57%); 67% were white. The 95 respondents were enrolled in 37 distinct phase I trials. Seventy of the 95 respondents (74%) were enrolled in protocols that included research biopsies; half of these were on trials with research biopsies that offered no benefit to the participants, and half were on trials with research biopsies that offered potential benefit. Nearly all respondents were familiar with biopsies; 89/95 (94%) had undergone biopsies previously for their cancer care. Forty-three respondents (45%) indicated that they had undergone bone marrow biopsies, 46 (48%) had undergone tumor biopsies, and one had undergone a hair follicle biopsy (data missing from five respondents). Of those who had tumor biopsies, 19 specified the location: head and neck (five); internal organ (nine); skin (two); breast (one); lymph node, location not specified (two).

Benefits of Research Biop sies

Nineteen of the 62 respondents (31%) who were asked about the benefit of a research biopsy (33 were not asked) demonstrated they understood the lack of benefit either by estimating the general benefit as zero or by including an altruistic benefit (help research or help others) in their estimation. The type of biopsy for the respondent's phase I trial and specifically whether it offered potential benefit was not associated with understanding (p = 0.42). Of all the respondents' characteristics and attitudes examined, those who thought they had a few treatment options left were more likely to misunderstand the lack of benefit of a research biopsy than those who thought they had hardly any or many options (p = 0.0355). Typical quotes by “misunderstanders” were “I assume that my treatment would be altered if the drug is not affecting my cancer,” and research biopsies “show if the drug is working or not. If it is not working, they will take me off the drug.” An “understander” who estimated 100% chance of benefit described the benefit altruistically: “Knowledge is the benefit. All will benefit from knowledge.” Another said, “The benefit of learning from somebody. They would be learning from me to benefit others.”

The 62 respondents asked about benefit made 83 comments (range 0–4). Five themes emerged from the coding of these comments: “help research,” “help others,” “help me later,” “help me now,” and “give me information now.” Eighty-six percent (54/62) mentioned benefits for self, including 25 (40%) who stated the research biopsy would “help me now,” another 25 (40%) who stated that it would “give me more information now,” and four (6%) who thought the biopsy would “help me later.” Another 19 (31%) saw the biopsy as a chance to help others or science, six (10%) reported no benefit at all, and four (6%) did not know or needed more information.

Forty-six percent—32 of the 70 respondents enrolled in trials with research biopsies—correctly identified the factual question whether the research biopsy on their trial was mandatory or optional; 15/70 (21%) did not know.

Risks of Research Biopsies

Respondents did not view research biopsies as risky. The means for each of the eight factors are listed in Table 1. Reversing the scores of the last four questions in Table 1 so that low risk was consistently represented by a low number, the overall mean score was 3.0. Of note, the mean perceived chance of a serious harm was low (2.2). Risk assessment was not associated with the acceptability of mandatory research biopsies, the willingness to undergo optional biopsies, or the understanding that research biopsies are not beneficial. When asked in an open-ended question to identify any concerns about research biopsies, 51/95 respondents (54%) had no concerns. The concerns mentioned by the others are reported in

Table 2, with immediate side effects, reported by 29/44 (64%), being the biggest concern. Respondents with more concerns considered research biopsies to be riskier ($p = 0.04$).

Acceptability of Mandatory Research Biopsies

The respondents thought that including research biopsies in clinical trials was acceptable. Only 17 respondents (18%) stated that a mandatory research biopsy as a component of a clinical trial would make them less likely to enroll in the trial, while 62 (65%) would agree to enroll in a trial that included a voluntary research biopsy. Forty-six respondents offered up to three comments about their voluntary research biopsy choice. Nearly half of the respondents mentioned altruistic reasons (25/46 [54%]). For example, as one respondent explained, “I've had so many, it's no big deal. I hope to help all of us. Helping research is my way of giving back.” Some of the comments also demonstrated a risk/benefit analysis: “It depends on how frequent the research biopsies are. I would have them just to help the doctors (unless they were once a week).” Another replied, “If they need that to do the study, then yes. The study is helping other people. The risk and pain of a biopsy can be controlled by staff.” Seventeen of the 46 respondents (37%) expected a voluntary research biopsy to help them now; 10 (59%) of these were enrolled in a phase I trial that included a potentially beneficial mandatory research biopsy, perhaps influencing their view.

Research Team

Twenty-two of 28 members of the research teams (79%; 12 physicians, one doctor of pharmacy, three nurse-practitioners, and six research coordinators) who had open phase I studies completed the survey. Four coordinators and two physicians with open phase I studies did not complete the survey.

Research team members estimated on average that 73% of patients recruited to participate in their clinical trials understood the nature of research biopsies. When asked in an open-ended question about how they responded when a patient did not understand, 20 investigators mentioned up to two strategies: explain again and then question the patient (4/20), contrast a research biopsy with clinical care (5/20), emphasize that the biopsy is for research (7/20), or point out its lack of benefit (2/20). In addition, one pointed out that the benefit is in the future, and one explained that the benefit is access to the trial.

Thirteen of the 22 investigators allowed us to observe 18 consent conversations with patients. Seventeen of these were conducted by a physician (often accompanied by a nurse or research coordinator), and one conversation was conducted by the phase I nurse-practitioner. Fifteen of the clinical trials discussed in these sessions included research biopsies, and three included only clinical biopsies. Of the 15 conversations about trials with research biopsies, four were too preliminary to discuss the details of the trial, three of the remaining 11 conversations (27%) clearly differentiated research from clinical biopsies, 4/11(36%) were fairly clear, and 4/11 (36%) were unclear. “Clear” conversations included comments like “Unfortunately, for this study, you know that it is an extra biopsy. You don't need to have this biopsy done ordinarily.” In the “fairly clear” conversations the research procedures and standard-of-care procedures were discussed separately, but it was never explicitly said that the research biopsies were not standard of care. “Unclear” conversations discussed the research biopsies within the discussion of standard-of-care procedures. For example, one unclear conversation discussed standard-of-care imaging scans, a clinical biopsy, and the research biopsy at the same time, with no distinction made among them.

Consent Document Review

We reviewed the consent forms for 37 distinct phase I trials in which respondents were enrolled. Nine were for trials with no biopsies, so these were excluded from the analysis of

the clarity of the discussion on research biopsies. Nineteen of the remaining 28 consent forms (68%) met our definition of unclear, and an additional six (21%) followed the NCI format—which we argue is unclear about research biopsies' potential for benefit or lack thereof—resulting in 25 consent forms (89%) that met our definition of unclear. The three clear consent documents had a separate section listing research-only procedures, or they listed all research-only procedures in the section on cost, explaining that these procedures would be paid for by the sponsor since they were for research only. In contrast, an example of an unclear consent form was one that carefully explained that the research biopsy would gauge the effect the study agent had on the cancer in the bone marrow but was silent about whether this had any impact on the research participant's clinical care.

Discussion and Conclusions

Respondents in our study who were enrolled in phase I clinical trials did not succeed in identifying the lack of benefit of a research biopsy. Only 31% either stated that the chance of benefit to them from this type of biopsy was zero or included an altruistic benefit in their estimation of benefit. Respondents were better able to identify whether the research biopsy on their individual trial was mandatory or optional (46%).

Among all the demographic characteristics and attitudes tested, only the respondent's view that he or she had a few treatment options—rather than hardly any or a lot—was associated with misunderstanding research biopsies. While this association might raise concerns that perceiving that one has few treatment options exacerbates therapeutic misconception, the respondents' view that he/she had hardly any treatment options was not associated with misunderstanding. The general lack of associations also differs from the usual finding that understanding is associated with demographic characteristics. Even groups who typically show better understanding of consent information—for instance, those who are younger and more educated[18]—were just as prone in this study to assign benefit to research biopsies. When asked to identify the benefits respondents hoped to get from the research biopsy, almost a third spontaneously mentioned an altruistic benefit, though personal benefit also ranked high, with 40% expecting the biopsy to help them now and 40% expecting information now, regardless of whether the biopsy on their trial would in fact help them or provide them with information. This spontaneous mention of altruism contrasts with previous studies of general phase I trial motivation and is particularly encouraging for trials with research biopsies. Truong and colleagues identified low levels of altruism in early-phase trials,[19] and Daugherty found that no one volunteered an altruistic motivation, although a third chose it from a list.[20]

Any conclusions about respondents' mistaken belief in individual benefit from research biopsies must be taken with caution since our sample size for this analysis (62) was reduced. Further, since some of our respondents were enrolled in clinical trials that did not include research biopsies, we asked all of them to consider a hypothetical research biopsy. This provided us with a standardized question, but we cannot be certain respondents were not thinking about the actual biopsy for their trial when expressing their views. However, there was no statistically significant difference in the answers provided when we analyzed the data by the type of biopsy for the trial in which respondents were enrolled ($p = 0.42$).

That two-thirds of respondents misunderstood the lack of benefit of a research biopsy is not unexpected for three reasons. First, investigators often did not make a clear distinction between research and standard-of-care procedures in their discussions with patients that we observed. However, since the consent process for a clinical trial often includes multiple conversations with a prospective participant, our one-time snapshot of these conversations is far from a total picture of the consent process, and unobserved conversations may have been

clearer. Second, although most investigators reported a reasonable strategy for combating misunderstanding about research biopsies, their overestimation of the number of phase I participants who understand the lack of benefit of such biopsies (73% compared to 31%) suggests that they do not easily identify misunderstanders. Third, the consent forms typically did not clearly identify what benefit the biopsy might offer. Only 3/28 (11%) clearly distinguished potentially beneficial from nonbeneficial research biopsies.

These observations point to three ways to increase understanding about research biopsies: 1) clarify consent documents with, for example, a chart that categorizes all the research procedures by possibility of medical benefit; 2) flag the page containing this chart, reminding the research team to discuss the chart with prospective trial participants; and 3) alert the research team to the potential for a high level of misunderstanding to motivate more explicit discussions with potential participants about research biopsies. Although enhanced consent forms have not yet been shown to improve understanding[21] and calls for improved methods of conveying information in the consent process are common,[22] a change in consent forms that targets just one aspect of information about a clinical trial may meet with more success. One physician commented that he had so many trials “in his head,” he did not want to explain the research biopsy without consulting the consent document. Thus, with some redesign, the form could serve two purposes: be a useful prompting tool for the research team and a source of information for patients recruited to enroll in the trial.

With regard to risk assessment, results were positive. These respondents—most of whom had undergone clinical biopsies—were very confident that benefits of research biopsies outweighed risks, that risks were well controlled, and that the knowledge to be gained from them was important. Biopsies were not seen as harmful or frightening, albeit somewhat painful. Respondents judged the chance of a serious harm to be low. Although there is not a lot of data in the literature on the risk of research biopsies, clinical biopsies have not been associated with undue risk,[23] so respondents' assessments of the low risk of research biopsies may be reasonable.

Respondents tended to view research biopsies as acceptable. Less than a fifth said that a mandatory biopsy would make them less likely to join a trial—fewer than the one-third reported in the Agulnik study[24]—and two-thirds reported that they would agree to undergo a voluntary biopsy. Over half of those who said they would decline a voluntary biopsy still mentioned the biopsy's benefit to science. Interestingly, the few negative comments—complaints of pain, dislike of research, and the wish that biopsies were not necessary—were made mostly by those who would undergo a voluntary biopsy. It is difficult to determine whether these statements indicate a lack of understanding of the term “voluntary” or were just expressions of negative associations about biopsies that were outweighed by other reasons to undergo the biopsy. Not surprisingly given respondents' willingness to undergo biopsies, over half had no concerns about them in the research context. The concerns mentioned by the others were mostly immediate side effects, although about a fifth thought there were too many research biopsies. Last, all of these respondents judged the importance of the knowledge to be gained from research biopsies as extremely high (9.5/10).

The findings about the acceptability of research biopsies raise a significant policy issue. Respondents' overall positive view of research biopsies and the knowledge they provide suggests that it is imperative for investigators and institutional review boards (IRBs) to review carefully the strength of the science supporting the biopsies and to require that the potential scientific benefit increases proportionately with the risk.[25] Some argue that biopsies often do not yield important knowledge,[26] though others disagree.[27] In any case, investigators and oversight bodies need to ensure that respondents' trust is well founded.

There are several limitations to this study. First, our respondents were all patients at a single academic cancer center, so their responses may not be generalizable outside of this setting. Second, because not all these respondents were enrolled in a clinical trial that included a research biopsy, we elicited their views based on a hypothetical description of a research biopsy. Responses to hypothetical vignettes do not directly correspond to choices and views in actual circumstances, so any conclusions about respondents' actual views about biopsies must be drawn with caution. However, studies suggest that respondents who are engaged and knowledgeable about a hypothetical vignette—as these respondents arguably were, since 94% had experienced a biopsy and all were enrolled in phase I trials—provide more thoughtful responses than disengaged respondents.[28] Third, although we instructed respondents to think about a "research biopsy," they may not have understood the distinction between research and clinical biopsies.

Our study is the first large-scale report about the views of research participants regarding the inclusion of research biopsies in clinical trials. Most of the respondents were enrolled in clinical trials that included a research biopsy. The perspectives of participants in trials with research biopsies can help inform the development of early-phase trials, as well as the development of other studies for which research biopsies are being considered. Participants' tendency to ascribe benefit to research biopsies calls for renewed efforts to carefully describe either research biopsies' potential benefit or lack thereof in consent conversations and documents, and their faith that these biopsies are not risky and will yield knowledge makes it imperative that scientists and regulators carefully design and review the studies that include research biopsies.

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Table 1

Psychometric Risk Questions

Risk	Mean (range for each was 0–10 unless noted)
Risk question stated so low risk is low number (0 none, 10 high)	
Chance of serious harm?	2.2
Chance of pain?	4.2
Harm of side effects?	3.6
Frightening?	2.5
Risk question stated so low risk is high number (0 not at all, 10 completely/high)	
How much do benefits exceed risks?	7.6 (1–10)
How well are risks known?	4.9
How well are risks controlled?	6.4
How important is knowledge to be obtained?	9.5 (5–10)

Table 2

Concerns with Research Biopsies

Concern	**#**
N = 44 (one to three concerns)	***(%) mentioning the concern***
Immediate side effects	29 (64%)
Long-term side effects	10 (22%)
Overuse of biopsies	8 (18%)
Lack of benefit	3 (7%)
Biopsy mandatory	3 (7%)
Who has access to tissue?	3 (7%)
Time biopsy takes	2 (4%)
Don't want to be part of research	2 (4%)